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(64) **NOVEL TANNIN COMPOSITION.**

(57) A novel tannin composition effective in treating mental diseases such as acute or chronic schizophrenia, which is represented by general formula (I). This composition can be prepared in a process comprising the steps of extracting rhubarb; subjecting the extract or its concentrate to gel filtration chromatography to obtain a methanol fraction; eluting the methanol fraction by gel filtration chromatography to obtain an eluate; subjecting the eluate to high-performance liquid chromatography to obtain a fraction eluted within a predetermined time; and removing the solvent from the eluted fraction. The tannin composition can be used as drug for treating mental diseases with no adverse effects.

**EP 0 216 936 A1**

A Novel Tannin CompositionTechnical Field

The present invention pertains to a novel tannin composition and, more particularly, to a novel tannin composition used for treating mental disorders such as acute and chronic schizophrenia and the like.

Background Art

Rhei Rhizoma is a kind of crude drug previously known, and used frequently in traditional chinese prescription (Kampo). The Rhei Rhizoma is so far known to possess an antibacterial effect, blood urea nitrogen-decreasing activity and anti-inflammatory effect. In the prior art, in order to obtain substances providing such effects, various compositions and/or compounds such as sennoside A have been isolated from Rhei Rhizoma. However, among the compounds isolated from Rhei Rhizoma, no components usable for treating mental disorders have been previously known at all.

Whereas, the following chemical compounds have been known as antipsychotic drugs used for treating schizophrenia:

Levomepromazine, chlorpromazine and thioridazine showing strong sedative effect; perphenazine, fluphenazine and haloperidol showing strong anti-hallucination and -delution effects; and sulpiride having mild sedative effect, and anti-hallucination and -delution effects. These drugs have been selectively used, according to their respective characteristics, in response to

patient's symptoms and the progress of disease. However, it has been well-known that these drugs produce adverse effects which are extrapyramidal syndrome such as muscle rigidity, dyskinesia and parkinsonism, and autonomic symptoms such as salivation, dry mouth and constipation. Consequently, a drug without adverse effects for treating mental disorders has long been desired to be developed.

#### Disclosure of Invention

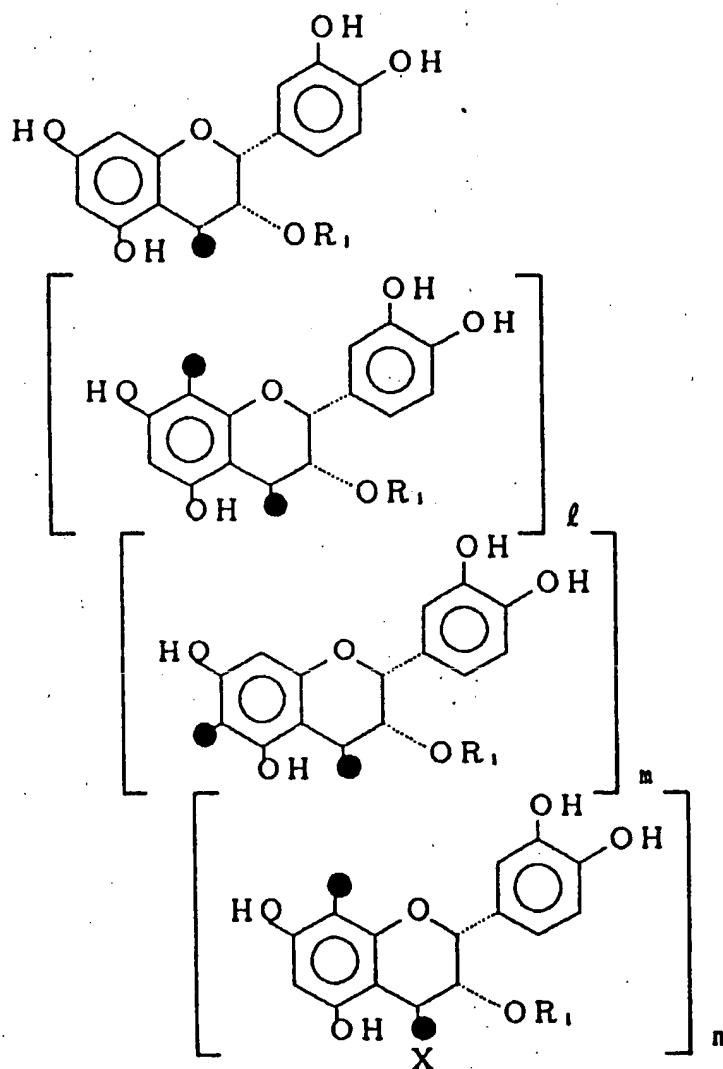
Therefore, one of the objects of the present invention is to provide a novel tannin composition.

Another object of the present invention is to provide a novel tannin composition extracted from Rhei Rhizoma.

A further object of the present invention is to provide such novel tannin composition having a potent antipsychotic effect, which can be used for treating acute and chronic schizophrenia, without causing any adverse effects.

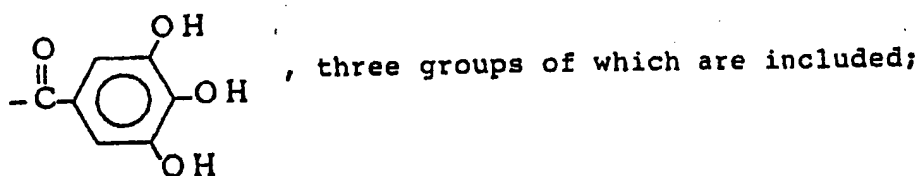
These and other objects, together with the advantages thereof over the prior art, will become apparent from the following description and the appended claims.

A novel tannin composition according to the present invention is represented by the following general structural formula:

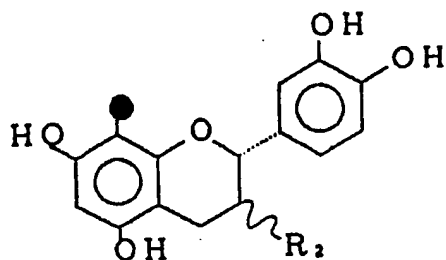


wherein  $l$  is an integer from 0 to 6,  $m$  is 0 or 1,  $n$  is an integer from 0 to 6, and  $l + m + n = 6$ ;

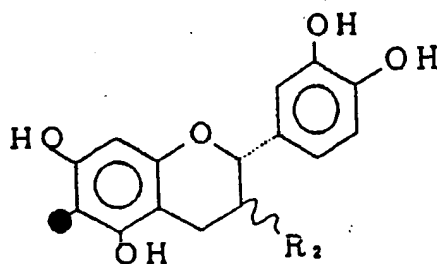
$R_1$  is hydrogen or G, G representing galloyl group



X is



or



$R_2$  is  $\text{OH}$ ,  $\dots \text{OG}$ , or  $\dots \text{OH}$ ; and filled dots  $\bullet$  mean bonding sites, and there is no possibly to bond between the mutual fourth positions in each unit, and there is only one bonding between the fourth position and the sixth position.

In accordance with the present invention, the above tannin composition may be obtained by the following steps:

obtaining an extractive from Rhei Rhizoma with water or an aqueous solution of an organic solvent;

separating said extractive or its concentrated liquid by gel filtration chromatography using water, an aqueous solution of ethanol, ethanol and methanol sequentially, to obtain a methanolic eluate;

separating said methanolic eluate, its concentrated liquid or dried solid by gel filtration chromatography with a mixture of at least two solvents selected from the group consisting of water, ethanol, methanol and acetone, to obtain an eluate;

subjecting said eluate to high performance liquid chromatography  
[column: Nucleosil 5C<sub>18</sub> (Macherey - Nagel) (4 X 250mm); mobile phase: 14-80% CH<sub>3</sub>CN/H<sub>2</sub>O (25mM oxalic acid); flow rate: 1ml/min; column temperature: 40°C], to separate and obtain a fraction eluted at the retention time from 10 to 25 minutes; and

removing the solvent from said eluted fraction;

It is also disclosed, according to the present invention, that the above tannin composition is effective in treating mental disorders such as acute and chronic schizophrenia.

#### Best Mode for Carrying Out the Invention

Rhei Rhizoma used in order to obtain a novel tannin composition according to the present invention is commercially

available in the form of crude drugs. The original plant of Rhei Rhizoma is perennial herb belonging to the Polygonaceae family.

Rhei Rhizoma is first extracted by using water or an aqueous solution of an organic solvent, in order to obtain a desired extractive. This extraction process is carried out at the temperature ranging from room temperature to the boiling point of the extracting solvent to be used. Preferably Rhei Rhizoma may be previously reduced to powders, and in this case high extracting efficiency is achieved. Ethanol, methanol, acetone and etc. are preferable as an extracting organic solvent. It is most recommendable to extract using water for 12 through 24 hours at room temperature. In this manner, the resultant extractive contains a minimum of contaminants other than the desired tannin composition of this invention. Repeating the above extraction process 2 through 4 times brings higher extracting efficiency.

The extractive obtained in the above extracting process may be directly subjected to gel filtration chromatography. Alternatively, the extractive may be concentrated prior to being subjected to the chromatography. Preferable examples of gel used in the gel filtration chromatography are Sephadex<sup>®</sup> (Pharmacia Fine Chemicals), MCI gel<sup>®</sup> (Mitsubishi Kasei) and  $\mu$ -Bondapak<sup>®</sup> (Waters Associates). Water, an aqueous solution of ethanol, ethanol and methanol are sequentially employed as eluting solvents. In case where MCI gel<sup>®</sup> or  $\mu$ -Bondapak<sup>®</sup> is used, methanol may be introduced immediately after water introduction. By this procedure, a methanol eluate is obtained.

The methanol eluate obtained in the above eluting process, its concentrated liquid or dried solid is subjected to gel filtration chromatography. An eluate is obtained in the chromatography by using a mixture of at least two solvents selected from the group consisting of water, ethanol, methanol and acetone. Preferable examples of packing gels employed are Sephadex<sup>®</sup> (Pharmacia Fine Chemicals), MCI gel<sup>®</sup> (Mitsubishi Kasei) and  $\mu$ -Bondapak<sup>®</sup> (Waters Associates). In case where Sephadex<sup>®</sup> is used as a packing gel, a mixture of ethanol, water and acetone is the most suitable solvent. In case where MCI gel<sup>®</sup> is packed in the column, a mixture of ethanol-water or methanol-water is the most suitable solvent. In this manner, a desired eluate is obtained.

The eluate obtained in the preceding process is subjected, as it is, to high performance liquid chromatography [column: Nucleosil 5C<sub>18</sub> (Macherey - Nagel) (4 X 250mm); mobile phase: 14-80% CH<sub>3</sub>CN/H<sub>2</sub>O (25mM oxalic acid); flow rate: 1ml/min; column temperature: 40°C].

And then a fraction eluted at the retention time from 10 to 25 minutes is separated to obtain a desired eluted fraction.

Lastly, the eluting solvent is removed by evaporation at reduced pressure from the fraction eluted in the preceding process, resulting in the separation of tannin composition according to the present invention.

Preferably examples of the pumps used in the above high performance liquid chromatography are TOYOSODA CCPD Dual Pump



(Toyosoda Kogyo), Waters 6000A-type Pump (Waters Associates), JASCO TRI ROTAR-VI Pump (Nihon Bunko Kogyo), Hitachi 655-type Pump (Hitachi Seisakusho), etc. In addition, preferable examples of the detectors used in the high performance liquid chromatography are TOYOSODA UV-8 Model II (Toyosoda Kogyo), Waters Model 440 Absorbance-detector (Waters Associates), JASCO UVIDEC-100-VI UV Spectrometer (Nihon Bunko Kogyo), Hitachi 638-41-type Variable-wavelength UV Monitor (Hitachi Seisakusho), etc. A suitable absorption wavelength in the detection is 280mm. A more detailed explanation regarding preparation of the tannin composition of the present invention is provided with the example hereinbelow.

#### Example

Powdered Rhei Rhizoma (3kg) was steeped in purified water (15-25 liters), and extracted at room temperature for 12-24 hours. The same extraction process was repeated three times to produce three same extractives. The combined extractives were concentrated to 4 liters at reduced pressure. This concentrate was subjected to column chromatography [Sephadex<sup>®</sup> LH-20 (Pharmacia Fine Chemicals 25-100 micrometers), (11 X 50cm)]. The column was eluted using water, water-ethanol (1:1), ethanol, methanol, acetone-water (1:1) (20 liters each) sequentially, and each fraction was obtained. The yields of these four fractions were 525, 193, 67, 47 grams, respectively.

The fraction No. 4 (36 grams) was subjected to column chromatography [Sephadex<sup>®</sup> LH-20, (5.8 X 50cm)], and the

column was eluted with a mixture of ethanol-water-aceton (1:0:0, 19:0.5:0.5, 18:1:1, 17:1.5:1.5, 16:2:2, 15:2.5:2.5, 14:3:3, 13:3.5:3.5, 12:4:4, 11:4.5:4.5, 10:5:5, 8:6:6, 0:1:1, 4 liters each). The eluate liquid was subjected to a high performance chromatography [pump: TOYOSODA CCPD Dual Pump; detector: TOYO SODA UV-8 Model II; column: Nucleosil 5C<sub>18</sub> (Macherey-Nagel) (4 x 250mm); mobile phase: 14-80% CH<sub>3</sub>CN/H<sub>2</sub>O (25mM oxalic acid); flow rate: 1millimeters/min; column temperature: 40°C; absorption: 280nm]. The fraction eluted at the retention time from 10 to 25 minutes was separated. The solvent was removed from the separated fraction by evaporation and 15.6 grams of the tannin composition of the present invention, was finally obtained.

#### Pharmacological Assessment

The test substance was dissolved in saline (0.9% NaCl) and administered i.p. or p.o. to rats in a single-dose study. To control group, only salines (i.p.) or water (p.o.) was administered.

#### Example 1

Eight male SD rats, 5-6 weeks of age, were used for each i.p. dose (0, 5, 10, 20 and 50mg/kg).

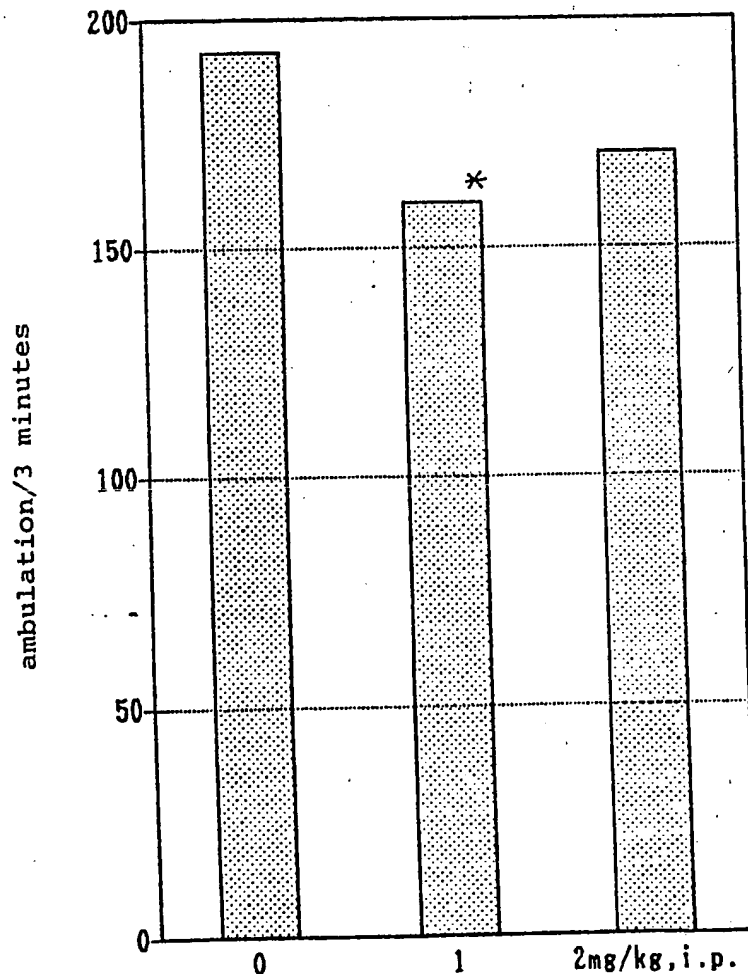
In the open field test, the test substance reduced the locomotor activity and rearing dose-dependently.

These suggest that the test substance has sedative effect.

Example 2

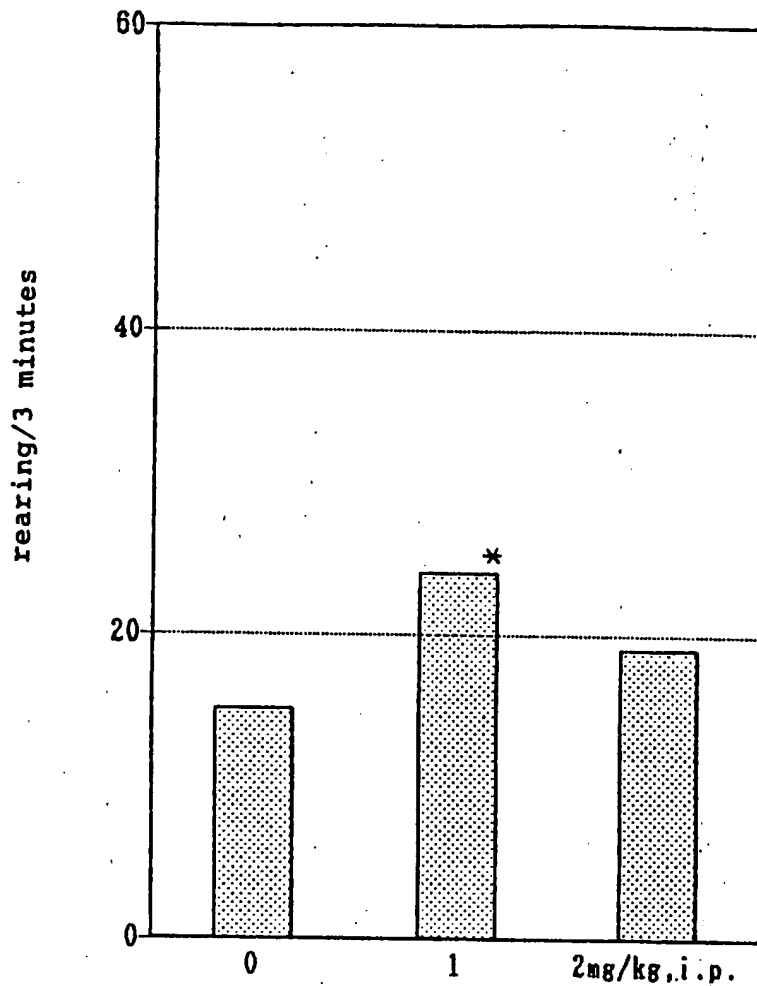
Eight male SD rats, 5-6 weeks of age, were used for each i.p. dose (0, 1 and 2mg/kg). The test substance was administered 1 hour prior to d-methamphetamine (1mg/kg, s.c.). d-Methamphetamine is known to produce abnormal behavioral in animals. The test substance at 1 and 2mg/kg inhibited d-methamphetamine-induced locomotor hyperactivity. (Graphs 1A and 1B)

Therefore, it is clearly indicated that the test substance has anti-methamphetamine effect. This inhibitory effect is twice as potent as chlorpromazine.



Graph 1A

\*  $p < 0.05$



Graph 1B

\*  $p < 0.05$ Example 3

Ten male Wistar-King A rats for each group, 5-6 weeks of age, were used. The olfactory bulbs of these rats were removed (O.B. rats), which resulted in the appearance of aggressive behavior. The effects of the test substance on aggressive behavior induced by olfactory bulbectomy were evaluated by the following 6 parameters;

1. attack: attack response to a rod presented in front of the snout.
2. tapping: jumping or startle response to tapping on the back.
3. pinching: flight response or attack response to tail pinching.

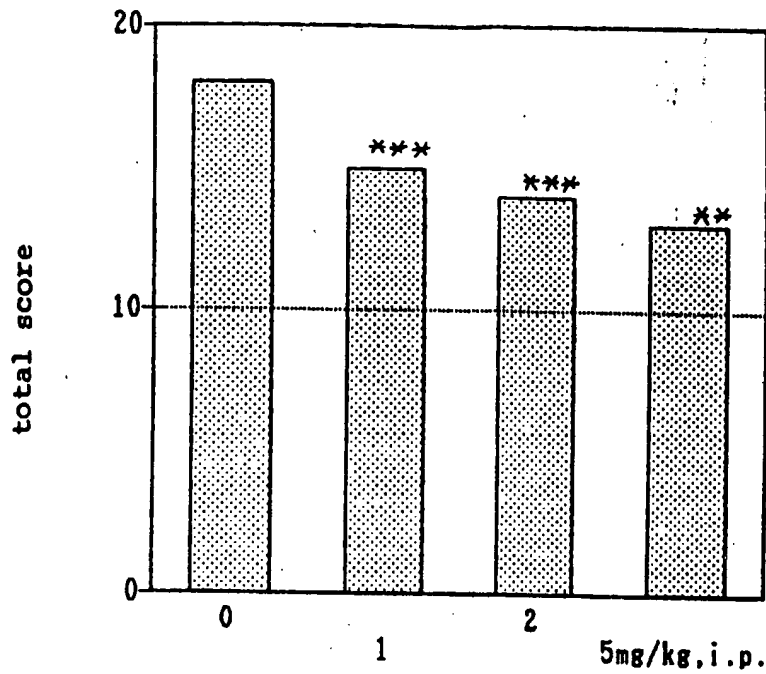
4. capture: struggle response to capturing.
5. vocal: vocalization during the observation period.
6. muricide: mouse killing behavior.

These parameters were graded on a 0-4 basis (score 0: no response - score 4: maximal response). The total score was made by summing up each score of 6 parameters. The test substance i.p. administered at 1, 2 and 5mg/kg significantly lowered total score of aggressive behaviors (Graph 2). This effect continued for up to about 6 hours. The test substance orally administered at 10 and 20mg/kg showed similar inhibitory effects to the above by i.p. administration.

These results suggest that the test substance has anti-aggressive effect.

This inhibitory effect is 10 times as strong as haloperidol and twice as strong as chlorpromazine.

During the above 3 experiments, catalepsy, ataxia and muscle relaxation were not observed.



Graph 2

\*\*  $p < 0.01$ \*\*\*  $p < 0.001$ 

#### Toxicological Assessment

LD<sub>50</sub> of the test substance in mice is as follows. The test substance was dissolved in saline except for oral administration (in water).

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Route of administration	LD <sub>50</sub> (mg/kg)
<hr/>	
intravenously administration	70.9
intraperitoneal administration	369.4
oral administration	> 1000
subcutaneous administration	> 1000

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The overall results obtained indicate the possibility that the test substance may be useful for some psychiatric disorders in human.

#### Practical Use

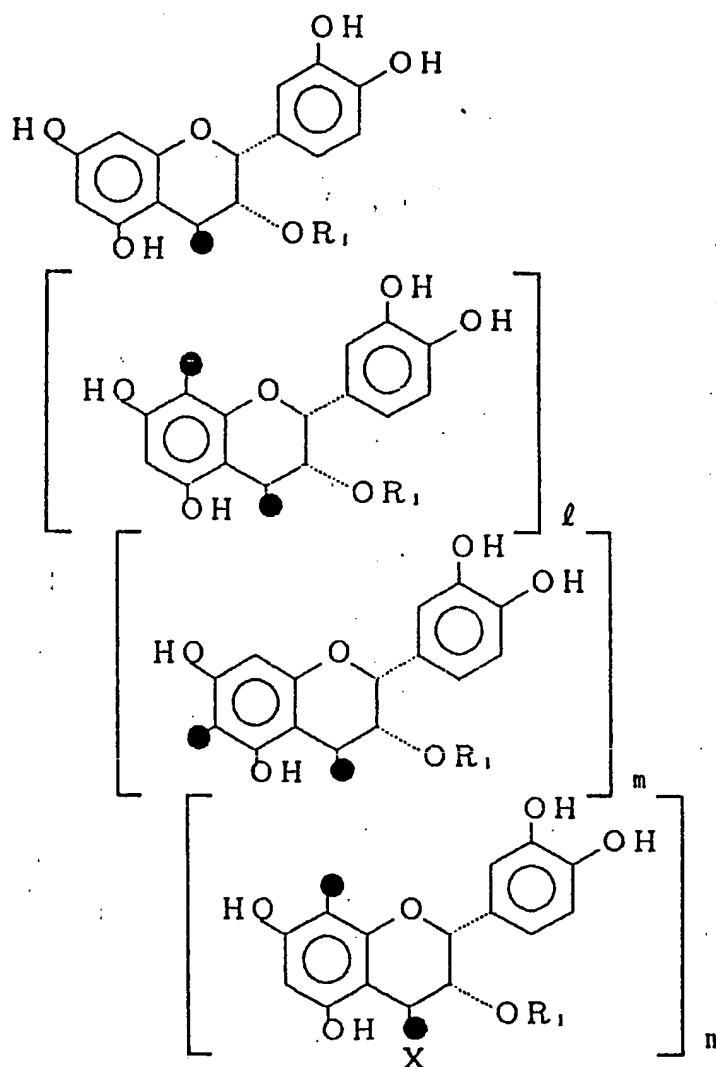
Medicines in the wide variety forms such as liquid, powder, granulated powder, pill, tablet, enteric coated tablet and capsule may be produced in the conventional manner by using this tannin composition together with suitable solvent, excipient, adjuvant and etc. The above medicines may be compounded into other medicinal active ingredient in case of prescribing. For oral administration, medicines in the form of liquid, powder, granulated powder, pill, tablet, enteric coated tablet and capsule may be prescribed by using at least one excipient such as starch, lactose, sucrose, mannitol and carboxymethylcellulose. The above medicines may also be produced by using brighteners such as magnesium stearic acid,

sodium lauric acid and talc; binders such as dextrin, crystalline cellulose, polyvinyl pyrrolidone and gelatin; and breaking agents such as potato starch and carboxymethylcellulose. This tannin composition may be administered as suspension, emulsion, syrup and elixior, which may contain taste and odor correcting agent and coloring agent.

In case of production of injecting medicines, there may be used diluents such as an injecting vegetable oil, propylene glycol and polyethylene glycol. Further, isotonic agents, stabilizer, antiseptics and anodynes may be added if necessary. It is preferable to dissolve the injecting medicines in a sterilized injecting medium.

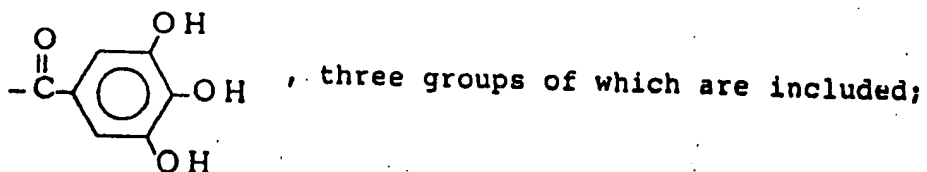


1. A novel tannin composition represented by the following general structural formula:

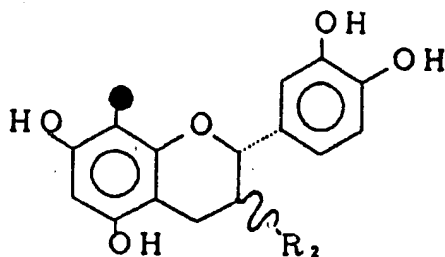


wherein  $l$  is an integer from 0 to 6,  $m$  is 0 or 1,  $n$  is an integer from 0 to 6, and  $l + m + n = 6$ ;

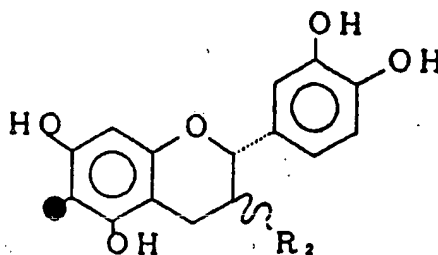
$R_1$  is hydrogen or G, G representing galloyl group



X is



or



$R_2$  is  $\triangleleft$  OH, . . . OG, or . . . OH; and filled dots  $\bullet$  mean bonding sites, and there is no possibility to bond between the mutual fourth positions in each unit, and there is only one bonding between the fourth position and the sixth position.

2. A novel tannin composition obtained by steps of:

obtaining an extractive from Rhei Rhizoma with water or an aqueous solution of an organic solvent;

separating said extractive or its concentrated liquid by gel filtration chromatography using water, an aqueous solution of ethanol, ethanol and methanol sequentially, to obtain a methanolic eluate;

separating said methanolic eluate, its concentrated liquid or dried solid by gel filtration chromatography with a mixture of at least two solvents selected from the group consisting of water, ethanol, methanol and acetone, to obtain an eluate;

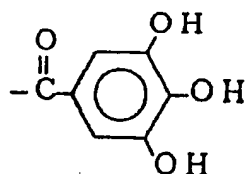
subjecting said eluate to high performance liquid chromatography column: Nucleosil 5C<sub>18</sub> (Macherey - Nagel) (4 X 250mm); mobile phase: 14-80% CH<sub>3</sub>CN/H<sub>2</sub>O (25mM oxalic acid); flow rate: 1ml/min; column temperature: 40°C , to separate and obtain a fraction eluted at the retention time from 10 to 25 minutes; and

removing the solvent from said eluted fraction;



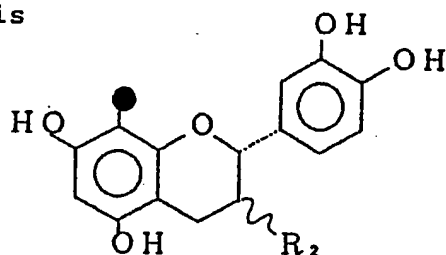
wherein  $l$  is an integer from 0 to 6,  $m$  is 0 or 1,  $n$  is an integer from 0 to 6,  $l + m + n = 6$ ;

$R_1$  is hydrogen or G, G represents galloyl group

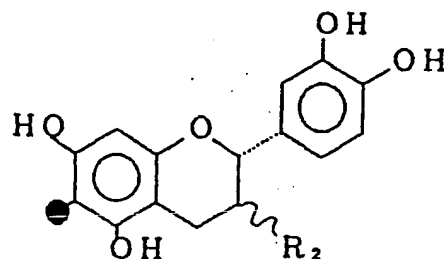


, three groups of which are included;

X is



or



$R_2$  is  $\text{OH}$ ,  $\text{OG}$ , or  $\text{OH}$ ; and filled dots  $\bullet$  mean a bonding sites, and there is no possibility to bond between the mutual fourth positions in each unit, and there is only one bonding between the fourth position and the sixth position.

3. An antipsychotic medicine usable for treating mental disorders such as acute and chronic schizophrenia and the like, which is comprising of a novel tannin composition obtained by steps of:

obtaining an extractive from Rhei Rhizoma with water or an aqueous solution of an organic solvent;

separating said extractive or its concentrated liquid by gel filtration chromatography using water, an aqueous solution of ethanol, ethanol and methanol sequentially, to obtain a methanolic eluate;

eluting said methanolic eluate, its concentrated liquid or dried solid by gel filtration chromatography with a mixture of at least two solvents selected from the group consisting of water, ethanol, methanol and acetone, to obtain an eluate;

subjecting said eluate to high performance liquid chromatography [column: Nucleosil 5C<sub>18</sub> (Macherey - Nagel) (4 X 250mm); mobile phase: 14-80% CH<sub>3</sub>CN/H<sub>2</sub>O (25mM oxalic acid); flow rate: 1ml/min; column temperature: 40°C], to separate and obtain a fraction eluted at the retention time from 10 to 25 minutes; and

removing the solvent from said eluted fraction;

$$\begin{array}{c}
 \text{HO} \quad \text{OH} \quad \text{OH} \\
 \diagup \quad \diagdown \quad \diagup \quad \diagdown \\
 \text{C}_6\text{H}_2 \text{---} \text{O} \text{---} \text{C}_6\text{H}_3(\text{OH})_2 \\
 \diagdown \quad \diagup \quad \diagdown \quad \diagup \\
 \text{OH} \quad \text{OR}_1
 \end{array}$$
  

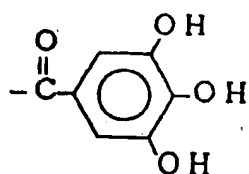
$$\left[ \begin{array}{c} \text{HO} \quad \text{OH} \quad \text{OH} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{C}_6\text{H}_2 \text{---} \text{O} \text{---} \text{C}_6\text{H}_3(\text{OH})_2 \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{OH} \quad \text{OR}_1 \end{array} \right]_l$$
  

$$\left[ \left[ \begin{array}{c} \text{HO} \quad \text{OH} \quad \text{OH} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{C}_6\text{H}_2 \text{---} \text{O} \text{---} \text{C}_6\text{H}_3(\text{OH})_2 \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{OH} \quad \text{OR}_1 \end{array} \right]_m \right]_n$$
  

$$\left[ \begin{array}{c} \text{HO} \quad \text{OH} \quad \text{OH} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{C}_6\text{H}_2 \text{---} \text{O} \text{---} \text{C}_6\text{H}_3(\text{OH})_2 \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{OH} \quad \text{OR}_1 \end{array} \right]_n$$

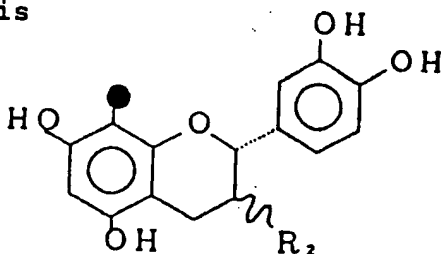
wherein  $l$  is an integer from 0 to 6,  $m$  is 0 or 1,  $n$  is an integer from 0 to 6,  $l + m + n = 6$ ;

$R_1$  is hydrogen or G, G represents galloyl group

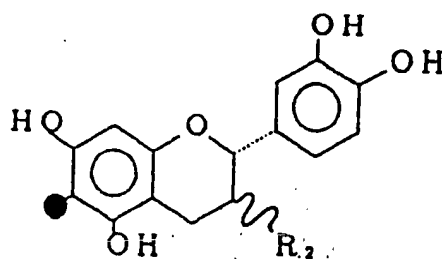


, three groups of which are included;

X is



or



$R_2$  is  $\triangleleft$  OH,  $\dots$ OG, or  $\dots$ OH; and filled dots  $\bullet$  mean a bonding sites, and there is no possibility to bond between the mutual fourth positions in each unit, and there is only one bonding between the fourth position and the sixth position.



## INTERNATIONAL SEARCH REPORT

0216936

International Application No.

PCT/JP86/00116

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)<sup>1</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl<sup>4</sup> C07D311/62, A61K31/35 //A61K31/78

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>2</sup>

Classification System

Classification Symbols

IPC

C07D311/62, A61K31/35, 31/78

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>3</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>11</sup>

Category <sup>12</sup>	Citation of Document, "with indication, where appropriate, of the relevant passages" <sup>13</sup>	Relevant to Claim No. <sup>14</sup>
X	JP, A, 58-154571 (Nippon Shinyaku Co., Ltd.) 14 September 1983 (14. 09. 83) Page 1, lower right column, formulae II and III (Family: none)	1
A	JP, A, 56-92283 (Hisamitsu Pharmaceutical Co., Inc.) 25 July 1981 (25. 07. 81) (Family: none)	1 - 2
A	JP, A, 58-32875 (Nippon Shinyaku Co., Ltd.) 25 February 1983 (25. 02. 83) (Family: none)	1
A	JP, A, 59-59638 (Nippon Shinyaku Co., Ltd.) 5 April 1984 (05. 04. 84) Page 3, lower left column, formula XIII (Family: none)	1

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is combined with one or more other such documents, such  
combination being obvious to a person skilled in the art<sup>25</sup> "Z" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search<sup>26</sup>

May 20, 1986 (20. 05. 86)

Date of Mailing of this International Search Report<sup>27</sup>

June 2, 1986 (02. 06. 86)

International Searching Authority<sup>28</sup>

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Signature of Authorized Officer<sup>29</sup>

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